AAU Association of American Universities
ACE American Council on Education
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February 3, 2003

Minh Thomas
Select Agent Program
Centers for Disease Control and Prevention
1600 Clifton Road, E-79
Atlanta, Georgia 30333

Dear Ms. Thomas:

We represent the presidents and chancellors, as well as senior administrators, of America's leading public and private universities, and are writing to comment on the Interim Final Rule on Possession, use, and Transfer of Select Agents and Toxins, 67 FR 76886. Many of our member universities perform research utilizing hazardous biological agents and toxins designated as "select agents" under Centers for Disease Control and Prevention (CDC) and Animal and Plant Health Inspection Service (APHIS) regulations. Accordingly, we have carefully reviewed the interim final rules published by both agencies in the December 13, 2002 *Federal Register*.

The university community supports Public Law 107-188, the Public Health Security and Bioterrorism Preparedness Response Act of 2002 (Law), and agrees with the Administration and Congress that the regulations to control the handling, storage, transfer, receipt, use of, and access to, select agents needed to be strengthened and expanded. At the same time, we believe that the research and education conducted by our member universities are a critical part of protecting the public from the threat of bioterrorism. These are the activities that will lead to the development of therapies for treating illness caused by select agents and to vaccines to protect the public from harm. We are committed to working with the federal government to ensure that hazardous agents and toxins are adequately secured, while ensuring that the conduct of research requiring access to hazardous materials by appropriately trained and screened persons is not unduly impeded.

In that spirit, we hope the enclosed comments will be of assistance as the CDC and APHIS prepare final regulations and begin implementing the new regulatory regime for select agents and toxins.

We support the following requirements of 42 CFR 73:

- We appreciate that required safety and security plans are largely performance-based. 42 CFR 73 establishes performance standards and allows entities to create individual plans to meet those standards. Regulations are most efficient and effective when they are performance-based so that entities can adopt the best compliance methods for their circumstance and institution.

- We believe the exclusion amounts per principal investigator for toxins in 73.4(f)(4) and 73.5(f)(4) are reasonable and protective of human health and the environment. We appreciate that quantity records are only required under 73.15(b)(2), (5) and (7) for toxins. It is not practical to record quantity information for viable agents.

We have the following comments on the interim rules, presented in order by section.

Part 73.0 – Applicability

We note that the February 7, 2003 effective date for the CDC regulations and the February 11, 2003 effective date for APHIS regulations are inconsistent. Since Sections 202(b) and (c) and 213(c) and (d) of the Law provide that the regulations are to become effective 60 days after they are promulgated, and the interim regulations were published in the Federal Register on December 13, 2002, the earliest effective date *for both* regulations should be February 11, 2003.

42 CFR 73.0(a) and (b) provides the compliance schedules for entities that on February 7, 2003, already are conducting activities under a certificate of registration issued under 42 CFR 72.6, or are lawfully in possession of agents or toxins as of such date. Section 73.0(c) provides compliance schedules for entities that as of February 7, 2003 are not already conducting activities under a Section 72.6 registration or are not already in lawful possession of agents or toxins. We assume that an entity may fall under Section 73.0(a) and (b) with respect to its registered or otherwise lawful activities, agents and toxins existing as of February 7, 2003, and the same entity may fall under Section 73.0(c) with respect to new activities, agents and toxins initiated after February 7. What is unclear, however, is how and when, after February 7, 2003, an entity can begin to use, acquire or create new agents or toxins, or begin new regulated activities, or allow new investigators (who may join the institution or the relevant project after February 7, 2003) to use existing agents and toxins or to join existing regulated activities.

Section 73.8 prohibits an entity from possessing, using or receiving agents or toxins, and prohibits individuals from having access to agents or toxins (and entities from allowing such access), unless they have received approval by the Secretary of HHS based on the Attorney General's security risk assessment approval of the entity, the RO, those who own or control the entity, and all individuals with access to agents and toxins. Section 73.0(c)(1) makes February 7, 2003 the effective date for all portions of Section 73.8 in connection with regulated activities that are not covered by a Section 72.6 registration and in connection with agents and toxins that are not otherwise lawfully possessed as of February 7, 2003. This seems to require that a security risk assessment approval be obtained before an entity or investigator can begin any regulated activities that were not already subject to a Section 72.6 registration, or before an entity can begin using an agent or toxin that was not already lawful possessed, as of February 7, 2003. Consequently, there appears to be a "black out" period beginning on February 7, 2003 during which new regulated activities cannot begin, new toxins or agents cannot be acquired, possessed, or transferred, and new investigators cannot begin work. It is unclear when that "black out" period ends, but this seems to be an unspecified time, which ends only when the Attorney General makes a decision on an application for approval.

The confusion is increased by Sections 73.0(c)(3) and (4). Section 73.0(c)(3) provides that the Section 73.7 prohibition against an entity's possession, receipt or transfer of agents and toxins without an approved registration under Section 73.7, becomes effective on November 12, 2003 in connection with regulated activities that are not already subject to a Section 72.6 registration, and in connection with agents and toxins that are not already otherwise lawfully possessed, as of February 7, 2003. Section 73.0(c)(4) then provides that from February 7, 2003, through November 11, 2003, an entity cannot conduct regulated activities that are not already covered by a Section 72.6 registration, or involve agents and toxins that are not already otherwise lawfully possessed, as of February 7, 2003, unless the entity has submitted a registration application package under Section 73.7 certifying compliance with Section 73.0(b)(2). That Section in turn prohibits regulated activities unless the entity submits security risk assessment approval applications to the Attorney General for the entity, the Responsible Official, and any individual who owns or controls the entity. It is unclear how Section 73.0(c)(1), which requires the security risk assessment approval to be received for the entity, RO, owners/controllers, and individuals with access is reconciled with Section 73.0(c)(4) which requires only that an application for security risk assessment approval be submitted and, even then, only for the entity, RO, and owners/controllers.

Recommendation: Clarify compliance schedules for activities regulated under 42 CFR 73 that begin between February 7, 2003 and November 11, 2003, and establish consistent effective dates for the regulations. Section 73.0(c) should be revised to clearly allow an entity to begin new activities, acquire new agents and toxins, and allow new investigations to begin work with agents and toxins at any time after February 7, 2003, provided that applications are first submitted under Sections 73.7 and 73.8.

Part 73.4 and 73.5 – HHS select agents and toxins

There are a number of inconsistencies between the CDC and APHIS definitions and treatments of certain select agents:

The definition of genetic elements is inconsistent for each regulation. For both CDC agents [42 CFR 73.4(e)(1)] and overlap agents [42 CFR 73.5(e)(1)], the CDC regulation limits the definition of genetic elements to viral nucleic acids that encode infectious or replication competent forms of the select agent viruses. The APHIS regulation provides the same definition for genetic elements of overlap agents [9 CFR 121.3(c)(1)]. However, genetic elements of animal agents are not defined, but are only addressed as exclusions from the regulation if the genetic elements are not capable of causing disease [9 CFR 121.3(f)(2)]. **We recommend that the CDC definition be adopted consistently and that 121.3(f)(2) be deleted.**

The inclusion of genetically modified listed agents is inconsistent between regulations. For both CDC agents [42 CFR 73.4(e)(3)] and overlap agents [42 CFR 73.5A(e)(3)], the CDC regulation specifies genetically modified listed agents as included in the requirements of the regulation. The APHIS regulation provides the same inclusion for genetically modified overlap agents [9 CFR 121.3(c)(3)], but does not state that genetically modified animal agents are included in the regulation. **We recommend the inclusion of genetically modified animal agents in the USDA regulation.**

The CDC regulation exempts the vaccine strain of Rift Valley fever virus (MP-12) and Venezuelan encephalitis virus strain TC-83 in the overlap agents category [42 CFR 73.5(f)(3)]. The APHIS regulation does not exempt those strains in its section of overlap agents. **We recommend the USDA regulation exempt both strains to be consistent with the CDC regulation.**

The definition of "agents" in recombinant DNA experiments that require approval by the HHS Secretary and/or the Administrator is not consistent. The CDC regulation specifies transfer of a drug resistance trait to select agents [42 CFR 73.10(c)(1)], whereas the APHIS regulation specifies transfer of a drug resistance trait to biological agents [9 CFR 121.10(c)(1)].

The CDC regulation requires approval by the HHS Secretary for only the transfer of a drug resistance trait [42 CFR 73.10(c)(1)]; the APHIS regulation requires approval for transfer of both a drug resistance trait and a pathogenic trait [9 CFR 121.10(c)(1)].

The definition of toxins in recombinant DNA experiments that require approval by the HHS Secretary and/or the Administrator is not consistent. The CDC regulation specifies formation of rDNA containing genes of select toxins [42 CFR 73.10(c)(12)], whereas the USDA regulation specifies toxins, not select toxins [9 CFR 121.10(c)(2)].

Recommendation: Clarify inconsistent treatment of certain select agents between CDC and APHIS regulations. We recommend that the definitions in the APHIS regulations be revised to match the CDC regulations by defining toxins as select agent toxins, and by defining biological agents as select agents. Also, we recommend changing APHIS regulations to require approval for transfer of only a drug resistance trait, to harmonize with the CDC regulation and the current NIH Guidelines on recombinant DNA research.

Part 73.7 - Registration

The CDC and APHIS regulations prohibit an entity from possessing or using select agents or toxins unless the entity has been granted a certificate of registration from the HHS Secretary or USDA Secretary [42 CFR 73.7, 7 CFR 331.6]. The CDC and APHIS will not issue a certificate of registration until the relevant agency has fully reviewed the entity's application and the Attorney General has completed a security risk assessment of the individuals listed in the application. [42 CFR 73.7-8, 7 CFR 331.6-7]

The regulations give specific timeframes by which an entity must submit its registration application as well as a list of individuals on whom the Attorney General must conduct background checks. An entity must be in full compliance with the regulations by November 12, 2003. [42 CFR 73.0, 7 CFR 331.0]

The regulations are silent, however, as to the time period in which the HHS or USDA Secretary and the Attorney General must complete their respective reviews and security assessments. A more troubling omission from the regulations is the failure to explain what happens to an entity's research when the Secretary or Attorney General fails to respond by the compliance deadlines. It

is conceivable that an entity could submit complete and accurate risk assessment and registration applications within the deadlines prescribed by the regulations and yet still not be in compliance because the relevant federal agencies fail to respond in a timely fashion, requiring the entity to halt research currently underway. Sections 202(c) and 213(d) of the Law require the regulations to apply effective dates in a manner that minimizes disruption of ongoing research and education.

Recommendation: Include a process by which an entity can continue its research with select agents and toxins until such time as the relevant government agencies complete their respective reviews and respond to the entity's applications for risk assessments and registrations.

Part 73.8 - Security Risk Assessment

Under the regulations, [deletion] in order to comply with 73.7 and 73.8, an entity must submit names and other requested information to the Attorney General on " . . . any individual who owns or controls the entity. . . ." [42 CFR 73.8(c), 7 CFR 331.6(b) (1)]

This requirement presents a unique challenge for universities. First, under most state laws governing the organization of nonprofit entities such as a university, there are no owners of the entity, i.e., no stockholders or partners, because the entity is organized for the good of the public, not for the good of the "stockholders" or "investors". Universities have trustees or regents, who are generally charged with overseeing their governance (but not day to day management) and who are charged to support the public purposes for which such entities are formed. Many states' attorneys general have oversight authority for such entities because they are organized for public purposes. No security purpose would be served by requiring that all such individuals be subject to background checks, as they are not involved in the oversight or management of select agent activities. We are concerned that an expansive interpretation of this provision would lead to additional delays by the Attorney General in completing the security risk assessments without any material security benefit. Likewise, the interpretation of "control" should be limited to those individuals who will have actual access to the select agents.

Recommendation: Clarify that at a university a security risk assessment must be obtained only for the Responsible Official and individuals who access a select agent or toxin.

Denials of access could result from something as common as the mistaken identity often seen in credit databases or from the need to employ someone whose efforts are required in the interest of public health and safety. 42 CFR 73.8 (e) provides that the Secretary of HHS may provide a limited approval for a specified time for individuals who otherwise meet the criteria of Section (d)(2) when circumstances warrant such action in the interest of public health and safety or national security. However there is no description of how this process would work and the length of time that would be required for such appeal.

Recommendation: Denial of access to select agents for any individual should be accompanied by a notice of the reasons for such denial. Further, a process for appeal of such a decision must be specified in the regulation.

It is not clear what information the entity must submit to the Attorney General to obtain a security risk assessment for individuals to have access to select agents, nor is it clear how the information is to be submitted. It is likely that institutional policies on privacy and certain federal or State laws will limit the information an entity may provide.

Recommendation: The final rules should define the information the entity must submit to the Attorney General for security risk assessments.

Part 73.10 – Safety

The Supplementary Information for this Part in the Federal Register announcement cites the CDC/NIH publications Biosafety in Microbiological and Biomedical Laboratories, and NIH Guidelines for Research Involving Recombinant DNA Molecules, as providing appropriate guidance to entities in developing and implementing safety plans. CDC further states, "We are seeking comments on the incorporation of these guidelines as requirements."

We believe incorporating these guidance documents as requirements in the final regulations would compromise their value and intent, and weaken the concept of a code of practice adopted by scientists, and health and safety professionals. The guidelines would soon lose current relevance because revisions would require rulemaking, which is a time-consuming process.

Therefore, we agree with the recommendation made by Howard Hughes Medical Institute, that the HHS Secretary not incorporate the Biosafety in Microbiological and Biomedical Laboratories and the NIH Guidelines for Research Involving Recombinant DNA Molecules as requirements in the final regulations. We recommend that the final regulations recognize these guidelines as authoritative codes of practice that entities should consider in developing and implementing a performance-based safety plan for the safe possession and use of select agents.

Part 73.11 – Security Plan

Although the majority of elements of the security requirements proposed under 42 CFR 73.11 are well intentioned, reasonable, and relatively straightforward to implement in an academic research environment, several items raise concerns about interpretation and application. These specific concerns include the definitions for several key terms and the implications for research operations.

We have specific concerns about several phrases and terms used to describe security controls, including the words "area" and "access". Our concerns relate to the interpretation of these terms as they apply to large, multi-disciplinary research laboratories where select agents may be used, but not as the sole or exclusive subject of research activity. Unfortunately, as currently written, it appears that the entire laboratory room, regardless of local security measures (i.e., locked box) will be considered a select agent "area." Such a designation will require everyone working in or otherwise accessing that room to either obtain security clearance and training, or be escorted and monitored at all times by a cleared individual while in the space. By defining "area" in their

security plan, entities will define the limits of their security measures. A specific delineation of "area" will aid entities, investigators and regulators. Entities should have the discretion to define "area," because the appropriate security measures will vary for each circumstance and institution.

Recommendation: Clarify that entities have discretion to define "area" in their security plans.

In other circumstances involving potentially hazardous materials (i.e., controlled substances, hazardous waste, radioactive materials), control is generally exerted at the point of storage and use rather than in the entire room or area where the materials may be stored or used. Primary security is the most important element, and must occur as close to the container or agent as possible, typically by a safe, lockable box, or lockable freezer or refrigerator, with per-use inventories kept for stock management and accountability. Room access restrictions apply only when the materials are in open use, but not when they are secured by lock or under an authorized individual's direct use. As for radioactive materials, everyone working in that room should receive specific safety awareness training and additional security information, and also be educated to challenge visitors. However, mandating background checks and extensive training are inappropriate for those who simply work or study in the vicinity but do not directly use select agents.

Provided that select agents are under direct supervised control while in use, and locked within a secure freezer, refrigerator, or other secondary container when not in use, it is not clear that the requirement for security, access control, and personnel background checks should apply to everyone else working in that room. To clarify this issue, we agree with comments made by the Howard Hughes Medical Institute (HHMI) that a definition of "access" would minimize uncertainty and help entities comply with the security, training, and record keeping requirements that rely on "access." We also agree with HHMI that the term "entry" rather than "access" be used when a requirement addresses access to an area where select agents and toxins are present.

If all persons working in the vicinity of a select agent must be subjected to the same provisions of access control, training, and security clearances, then the populations potentially affected by these regulations will greatly expand. A broader definition of access will create significant logistical and financial burdens since many research groups often share specialized equipment and instrumentation, often in different rooms. Segregating functions and equipment may force researchers to procure and dedicate duplicate equipment and analytical instrumentation so that work with select agents can be completely isolated and segregated from all other activities. An over-broad definition of access also is likely to prevent important collaboration among researchers that often leads to scientific discoveries, without providing meaningful security benefits.

Recommendation: 42 CFR 73 should include a definition of "access" to mean: "The ability to gain physical control of select agents and toxins."

Package Inspections

The requirement under 42 CFR 73.11(d)(4) to inspect all packages upon entry to and exit from the select agent area is unclear. What is the definition of a package? For example, does it include shipping packages, containers, personal luggage, or any wrapped or covered device or container? Are packages exclusively those containing select agent samples, or any carrier or container brought into or out of the area? It would not be practical to inspect the many packages of laboratory materials and infectious waste that enter and exit the laboratory. If the intent of this section is to address only select agent packages, then precedent for inspecting shipments and transfers already exists through the EA-101 Select Agent Transfer Forms and need not change. **Recommendation: Clarify that the inspection requirement only applies to packages used for the shipment or transfer of select agents or toxins. Also, clarify who should perform these inspections.**

Part 73.13 – Training

We appreciate HHS's interest in avoiding unnecessary duplicative training. However, we do not agree that Bloodborne Pathogen training is a suitable substitute for training specific to the use of select agents.

Recommendation: Revise this section to require training in safe use of select agents commensurate with the individual's level of access, and specify that such training need not duplicate training provided under the OSHA Bloodborne Pathogen Standards.

Part 73.15 – Records

Many of the detailed record-keeping requirements of these sections, which are to become effective on February 7, 2003, are directly tied to, and will be implemented through, the security plan's physical facility security and other requirements. However, the security plan will not be developed until June 12, 2003 and will not be implemented until September 12, 2003. It will be very difficult for institutions to comply with record-keeping requirements that are tied to physical security and other security plan requirements before the security infrastructure under the plan is developed and in place.

For example, under the Sections 73.11 and 331.11 of the respective regulations, an entity must provide secure areas where agents and toxins are stored or used, and the security plan must include an inventory of toxins and agents. Entities will need to define such areas and then implement access and other security controls to segregate them, as well as to determine how the new inventory controls will be administered. It may be necessary for some entities to make physical changes to facilities, and the June and September 2003 effective dates for development and implementation of the security plan provide at least some time to do so. Under Sections 73.15 and 331.14 of the respective regulations on record-keeping, detailed inventories of agents/toxins, as well as records on access to areas where agents and toxins are used or stored, must be kept. Yet, the manner of administering the inventories to support security and the definition of the areas where agents and toxins are used or stored will be defined under the security plan.

Recommendation: The effective date under Sections 73.0(a)(1) and 331.0 for the record keeping requirements of Sections 73.15 and 331.14 should be September 12, 2003, to coincide with the effective date under Sections 73.0(a)(5) and 331.0(e) for implementation of the security plan under Sections 73.11 and 331.11.

This section also states "The Responsible Official must maintain complete records relating to the activities covered by this Part." Depending on the level of the official designated to be the RO, as well as the size and decentralized nature of the entity, the records may be more effectively maintained elsewhere. Flexibility will allow each entity to determine the most effective manner of reliable record keeping. For example, if an institution designates a Vice President for Research as the RO, it would be more effective to have the institutional Biosafety Officer maintain the records.

Recommendation: This section be revised to state "The Responsible Official shall ensure that complete records relating to the activities covered by this Part are maintained."

Part 73.16 – Inspections

While it may be necessary for the federal departments to review compliance with the new regulations or conduct unannounced inspections, a background in financial auditing alone is insufficient to review and critique the scientific practices and procedures involved.

Recommendation: Biosafety and biosecurity inspection teams should include professionals who have been educated and trained in, and have significant experience in, these multidisciplinary fields.

General Comments on Cost of Compliance

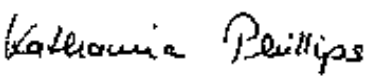
In its Federal Register notice, APHIS notes that "the costs associated with this rule could be considerable" while CDC in its notice indicates that "any costs of compliance should not be significant." CDC's 42 CFR Part 73 draft Regulatory Impact Analysis (Exhibit 4-1) reports the Average Annualized Cost per Lab for a "large" university to be $153,400. We respectfully submit that the costs will, indeed, be quite significant, exceeding the CDC estimate. For example, at one university in 2002, HHS' Office of Inspector General recommended over $400,000 in specific security improvements for one 1,000 square foot Biosafety Level 3 select agent laboratory and the building in which it is located. This university has other facilities where select agent research is conducted, so its costs will far exceed the CDC estimate. Several other large universities estimate that the costs over the next several years for facilities and staff to be in full compliance with the new regulations will greatly exceed the CDC estimates.

We wholeheartedly agree with the CDC regulatory benefits analysis that adequate security for select agents is crucial to protect public health and safety, and that the potential costs of accidental or intentional release of a select agent or toxin could far exceed the costs institutions will incur to implement these new regulations. However, that does not address the issue of how institutions will find the immediate funding sources needed to comply. Facilities and

Administrative cost rates (F&A) at universities cannot be immediately adjusted to absorb these major new costs, universities only partially recover their current F&A costs, and additional administrative costs for almost all major research universities cannot be recovered because of a government imposed cap on such costs. We recommend that select agent infrastructure support grants be made available for institutions to offset some of the added compliance costs.

Please contact us if you have any questions or wish to discuss our concerns in more detail.

Cordially,



Nils Hasselmo
President
Association of
American Universities

David Ward
President
American Council
on Education

Katharina Phillips
President
Council on
Governmental Relations